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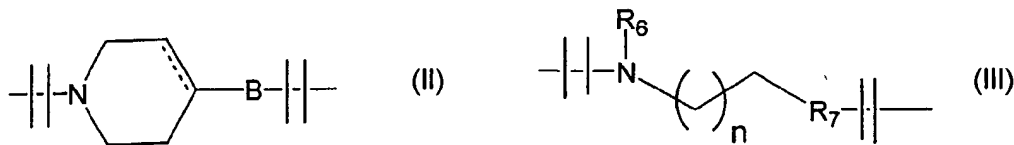
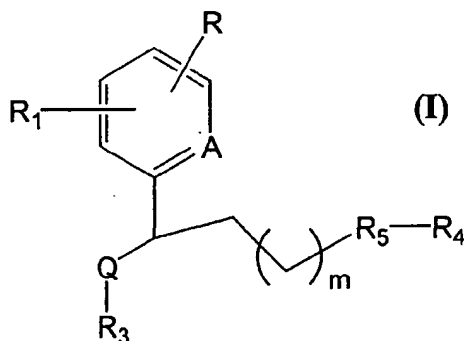
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(54) Title: PHENYLALKYLAMINES AND PYRIDYLALKYLAMINES



(57) **Abstract:** Compounds of formula (I): (A is CH or N, R and R₁ are a wide range of substituents, Q is CO, CHOH or CHOR₂, R₂ is alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted, or is alkanoyl, alkanoyoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminothiocarbonyl, alkylaminothiocarbonyl or dialkylaminothiocarbonyl, R₃ is H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted, m is 1 or 2, R₄ is an aryl or heteroaryl group, either of which is optionally substituted, R₅ is either (II) or (III), wherein m is 1 or 2, R₆ is H or alkyl, R₇ is O, S, NR₆ or CH₂, B is a bond, O, S, NR₆ or CH₂ and ----- represents a single or double bond) have affinity for serotonergic receptors. These compounds and their enantiomers, diastereoisomers, N-piperazine oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT_{1A} receptor activity.



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

TITLE**Phenylalkylamines and Pyridylalkylamines****DESCRIPTION**

The invention relates to phenylalkylamines and pyridylalkylamines having affinity for serotonergic receptors, pharmaceutical compositions thereof and uses for such compounds and compositions.

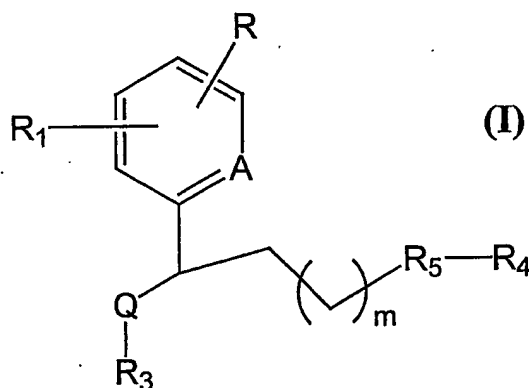
In mammals, micturition (urination) is a complex process that requires the integrated action of the bladder, its internal and external sphincters, the musculature of the pelvic floor and neurological control over these muscles at three levels (in the bladder wall or sphincter itself, in the autonomic centres of the spinal cord and in the central nervous system at the level of the pontine micturition centre (PMC) in the brainstem (pons) under the control of the cerebral cortex) (De Groat, *Neurobiology of Incontinence*, Ciba Foundation Symposium 151:27, 1990). Micturition results from contraction of the detrusor muscle, which consists of interlacing smooth-muscle fibres, under the control of the parasympathetic autonomic system originating from the sacral spinal cord. A simple voiding reflex is triggered by sensory nerves for pain, temperature and distension that run from the bladder to the sacral spinal cord. However, sensory tracts from the bladder reach the PMC too, generating nerve impulses that normally suppress the sacral spinal suppression of cortical inhibition of the reflex arc, and relaxing the muscles of the pelvic floor and external sphincter. Finally, the detrusor muscle contracts and voiding occurs. Abnormalities of lower-urinary tract function, e.g. dysuria, incontinence and enuresis, are common in the general population. Dysuria includes urinary frequency, nocturia and urgency, and may be caused by cystitis (including interstitial cystitis), prostatitis or benign prostatic hyperplasia (BPH) (which affects about 70% of elderly males), or by neurological disorders. Incontinence syndromes include stress incontinence, urgency incontinence, overflow incontinence and mixed incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

Previously, treatment of neuromuscular dysfunction of the lower urinary tract involved administration of compounds that act directly on the bladder muscles, such as flavoxate, a spasmolytic drug (Ruffman, *J. Int. Med. Res.* 16:317, 1988) which is also active on the PMC (Guarneri *et al.*, *Drugs of Today*, 30:91, 1994), or anticholinergic compounds such as oxybutynin (Andersson, *Drugs* 36:477, 1988) and tolterodine

(Nilvebrant, *Life Sci.* **68**(22-23): 2549, 2001). The use of α 1-adrenergic receptor antagonists for the treatment of BPH is common too, but is based on a different mechanism of action (Lepor, *Urology*, **42**:483, 1993). However, treatments that involve direct inhibition of the pelvic musculature (including the detrusor muscle) may have unwanted side effects, such as incomplete voiding or accommodation paralysis, tachycardia and dry mouth (Andersson, *Drugs* **35**:477, 1988). Thus, it would be preferable to utilize compounds that act via the central nervous system to, for example, affect the sacral spinal reflex and/or the PMC inhibition pathways in a manner that restores normal functioning of the micturition mechanism.

EP 0982304 discloses 5-HT_{1A} binding agents which may be used in the treatment of CNS disorders, such as depression.

The invention provides compounds of formula I



wherein

R represents a hydrogen atom or one or more substituents selected from the group consisting of (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkylthio, hydroxy, halo, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₆)-haloalkyl, (C₁-C₆)-haloalkoxy, (C₁-C₆)-hydroxyalkyl, alkoxy-(C₁-C₆)-alkyl, nitro, amino, (C₁-C₆)-aminoalkyl, N-(C₁-C₆)-alkylamino, N-(C₁-C₆)-alkylamino-(C₁-C₆)-alkyl, N, N-di-(C₁-C₆)-alkylamino, acylamino, (C₁-C₆)-alkylsulphonylamino, aminosulphonyl, (C₁-C₆)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(C₁-C₆)-alkylaminocarbonyl, N, N-di-(C₁-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, alkylcarbonyl-(C₁-C₆)-alkyl, formyl, alkanoyloxy-(C₁-C₆)-alkyl, (C₁-C₆)-alkylaminocarbonylamino, (C₁-C₆)-alkylsulphinyl, (C₁-C₆)-alkylsulphonyl, and N, N-di-(C₁-C₆)-alkylaminosulphonyl groups;

R₁ is selected from the group consisting of hydrogen, cycloalkyl, aryl, aryloxy,

aralkyl, aralalkoxy, heterocyclic, heterocycloxy, heterocycloalkyl and heterocycloalkoxy groups, each group being optionally substituted with one or more substituent R, defined as above;

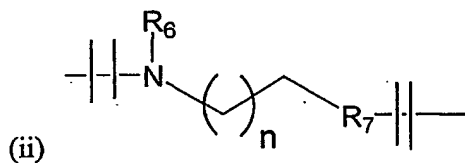
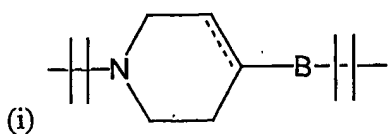
Q represents $-C(O)-$ or $-CH(OR_2)-$ where R_2 represents a member selected from the group consisting of hydrogen, (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl and cycloalkyl groups, wherein each group is optionally substituted with one or more groups selected from R_8 or R_9 , where R_8 is selected from the group consisting of halo, (C_1-C_6) -alkoxy, (C_1-C_6) -haloalkoxy, cyano, (C_1-C_6) -alkoxycarbonyl, (C_1-C_6) -alkylcarbonyl, alkoxyalkyl, aminocarbonyl, $N-(C_1-C_6)$ -alkylaminocarbonyl, N, N -di- (C_1-C_6) -alkylaminocarbonyl groups and R_9 is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, and heteroarylalkoxy groups, each optionally substituted with R, or R_2 represents $-C(O)-(C_1-C_6)$ -alkyl, $-C(O)O-(C_1-C_6)$ -alkyl, $-C(O)NR_{10}R_{11}$ or $-C(S)NR_{10}R_{11}$ wherein R_{10} and R_{11} are independently hydrogen or (C_1-C_6) -alkyl;

R_3 represents (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl, cycloalkyl, aryl or heterocycle, each being optionally substituted with one or more substituent R or R_1 , defined as above;

R_4 represents aryl or heterocyclic, each being optionally substituted with one or more substituents R, defined as above;

A represents CH or N,

R_5 represents group (i) or group (ii)



(where R_4 is bound to the right of each group)

m and n are independently 1 or 2,

R_6 represents H or alkyl,

R_7 represents O, S, NR_6 or CH_2 ;

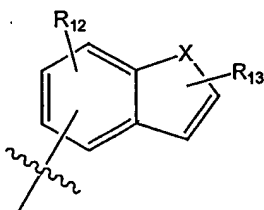
B represents a bond, O, S, NR_6 or CH_2 ; and

----- represents a single or double bond,

or an enantiomer, optical isomer, diastereomer, N-oxide (e.g., N-piperidine oxide), crystalline form, hydrate, solvate or pharmaceutically acceptable salt thereof.

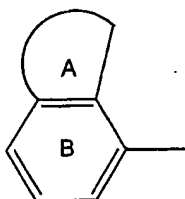
In certain embodiments, the invention provides compounds of formula I with the

proviso that the substituents of formula I are not such that simultaneously Q represents $C(O)-$ or $-CH(OR_2)-$ where R_2 represents hydrogen; R represents a hydrogen atom or one or more substituents selected from the group consisting of (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, (C_1-C_6) -alkylthio, hydroxy, halo, (C_1-C_6) -haloalkyl, nitro, amino and cyano groups; R_1 is selected from the group consisting of hydrogen, unsubstituted phenyl, and alkylphenyl groups; R_3 represents cycloalkyl, aryl or heterocycle, each being optionally substituted with one or more substituent selected from the group consisting of (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy, (C_1-C_6) -alkylthio, hydroxy, halo, (C_1-C_6) -haloalkyl, nitro, amino, cyano, unsubstituted phenyl, and alkylphenyl groups; R_5 represents group (i) wherein B represents a bond or CH_2 ; and R_4 represents the group



wherein X represents O, S, NH, $N(C_1-C_6\text{-alkyl})$, $S(=O)$ or $S(=O)_2$, and R_{12} and R_{13} each represent one or more member selected independently from the group consisting of halo, hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, nitro, amino, cyano, $N-(C_1-C_6)$ -alkylamino, $N, N\text{-di-}(C_1-C_6)$ -alkylamino, aminocarbonyl, $N-(C_1-C_6)$ -alkylaminocarbonyl, $N, N\text{-di-}(C_1-C_6)$ -alkylaminocarbonyl and acylamino groups.

In certain embodiments, the invention provides compounds of formula I with the proviso that the substituents of formula I are not such that simultaneously Q represents $C(O)-$; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, $N, N\text{-di-alkylamino}$, aminocarbonyl and alkoxycarbonyl groups; R_1 represents hydrogen; R_5 represents group (i) wherein B represents a bond or CH_2 ; R_4 represents an aryl or fully aromatic heteroaryl, each optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, $N, N\text{-di-alkylamino}$, aminocarbonyl and alkoxycarbonyl groups, or R_4 represents a bicyclic heteroaryl radical of formula



wherein A is a saturated or unsaturated ring having one or more heteroatoms, where rings A and B are each independently substituted with one or more substituent selected from the group consisting of alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, alkanoyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, , amino, N-alkylamino and N,N,- di-alkylamino; and R₃ represents a saturated heterocyclic ring comprising a nitrogen atom, through which said saturated heterocyclic ring is bonded to the adjacent carbonyl group at Q, and which may optionally include a further hetero atom, and which may also be optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo and haloalkyl groups.

Preferred compounds of the invention include those whose preparation is described in the Examples below.

Compounds of formula I can exist as four stereoisomers, which may be present in racemic mixtures or in any other combination. Racemic mixtures can be resolved, i.e., subjected to enantiomeric enrichment, to yield compositions enriched with a particular enantiomer. Enantiomeric enrichment can be expressed as ee (enantiomeric excess) as defined below.

The invention also includes metabolites of the foregoing compounds having the same type of activity, hereinafter referred to as active metabolites.

The invention also contemplates prodrugs which are metabolized in the body to generate any of the foregoing compounds.

In another embodiment, the invention provides pharmaceutical compositions comprising compounds of formula I, enantiomers, diastereomers, N-oxides, crystalline forms, hydrates, solvates or pharmaceutically acceptable salts of such compounds of formula I, in admixture with pharmaceutically acceptable diluents or carriers such as those disclosed.

Yet another embodiment is a method for reducing the frequency of bladder contractions due to bladder distension in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to reduce the frequency of bladder contractions due to bladder distension to the mammal.

Yet another embodiment is a method for increasing urinary bladder capacity in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to increase urinary bladder capacity to the mammal.

Yet another embodiment is a method for treating disorders of the urinary tract in a mammal (such as a human) in need thereof by administering an effective amount of at least one compound of the present invention to ameliorate at least one condition among urinary urgency, overactive bladder, increased urinary frequency, decreased urinary compliance (decreased bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder.

In yet other embodiments, the invention provides for methods of treating the above disorders, by administering a compound of formula I in combination with other agents such as, for example, one or more additional 5HT_{1A} antagonist, antimuscarinic drugs, α 1-adrenergic antagonists, inhibitors of the cyclooxygenase enzyme, which may inhibit both COX1 and COX2 isozymes or which may, alternatively, be selective for COX2 isozyme, and NO donor derivatives thereof.

In yet another embodiment, the present invention provides a method for treating a mammal suffering from a central nervous system (CNS) disorder manifest in a serotonergic dysfunction by administering an effective amount of at least one compound of the present invention to treat the CNS disorder. Such dysfunctions include, but are not limited to, anxiety, depression, hypertension, sleep/wake cycle disorders, feeding disorders, behaviour disorders, sexual dysfunction and cognition disorders in mammals (particularly in humans) associated with stroke, injury, dementia, and originated by neurological development, attention-deficit hyperactivity disorders (ADHD), drug addiction, drug withdrawal, irritable-bowel syndrome. Treatment may be effected by delivering a compound of the invention to the environment of a 5-HT_{1A} serotonergic receptor, for example, to the extracellular medium (or by systemically or locally administering the compound to a mammal possessing such receptor) an amount of a compound of the invention effective to increase the duration of bladder quiescence with no contractions.

COMPOUNDS

The invention relates to compounds of formula I as disclosed above. The invention includes the enantiomers, diastereoisomers, N-oxides, crystalline forms, hydrates, solvates or pharmaceutically acceptable salts of these compounds, as well as active metabolites of these compounds having the same type of activity.

The term "haloalkyl" includes alkyl groups substituted by a single halogen atom (monohaloalkyl) and those substituted by more than one halogen atom (polyhaloalkyl). Examples of the latter are trifluoromethyl and 2,2,2-trifluoroethyl groups. The term haloalkoxy is to be interpreted correspondingly. Preferred haloalkoxy groups include trifluoromethoxy and 2,2,2-trifluoroethoxy groups.

The term "aryl", alone or in combination, refers to a carbocyclic aromatic system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as phenyl, naphthyl, tetrahydronaphthyl, indane and biphenyl.

The terms "heterocyclic" and "heterocyclo" refer to saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be selected from nitrogen, sulphur and oxygen. Examples of saturated heterocyclic radicals include saturated heteromonocyclic groups containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl); saturated heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., morpholinyl); saturated heteromonocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl). Examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole.

The terms "heterocyclo" and "heterocyclic" encompass the term "heteroaryl," which refers to unsaturated heterocyclic radicals. Examples of "heteroaryl" radicals include unsaturated 5 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl) tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl); unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (e.g., tetrazolo[1,5-b]pyridazinyl); unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulphur atom, for example, 2-thienyl, 3-thienyl; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (e.g., benzoxazolyl, benzoxadiazolyl); unsaturated 5 to 6-membered

heteromonocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 sulphur atoms and 1 to 3 nitrogen atoms (e.g., benzothiazolyl, benzothiadiazolyl) and the like. The term "heteroaryl" also refers to radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. Said "heterocyclic group" may have 1 to 3 substituents such as, for example and without limitation, lower alkyl, hydroxy, oxo, amino and lower alkylamino. Preferred heterocyclic radicals include five to ten membered fused or unfused radicals. Examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl, benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, and pyrazinyl.

The term "cycloalkyl" refers to saturated carbocyclic radicals having three to ten carbon atoms. Preferred cycloalkyl radicals are "lower cycloalkyl" radicals having three to seven carbon atoms. Examples include radicals such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A most preferred cycloalkyl group is cyclohexyl.

The term "acyl", whether used alone, or within a term such as "acylamino", denotes a radical provided by the residue after removal of hydroxyl from a carboxylic acid. Preferred acyl groups are alkanoyl groups, such as acetyl.

A "metabolite" of a compound disclosed herein is a derivative of a compound which is formed when the compound is metabolized. The term "active metabolite" refers to a biologically active derivative of a compound that is formed when the compound is metabolised. The term "metabolized" refers to the sum of the processes by which a particular substance is changed in the living body. All compounds present in the body are manipulated by enzymes within the body in order to derive energy and/or to remove them from the body. Specific enzymes produce specific structural alterations to the compound. Cytochrome P450, for example, catalyses a variety of oxidative and reductive reactions. Uridine diphosphate glucuronyltransferases, for example, catalyse the transfer of an activated glucuronic-acid molecule to aromatic alcohols, aliphatic alcohols, carboxylic acids, amines and free sulphhydryl groups. Further information on metabolism may be obtained from *The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill (1996), pages 11-17.

The metabolites of the compounds disclosed herein can be identified either by administration of compounds to a host and analysis of tissue samples from the host, or by incubation of compounds with hepatic cells or other *in vitro* systems such as cytochromes or microsomes, and analysis of the resulting compounds. Both methods are well known in the art.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. As used herein, the term "optical isomer" is equivalent to the term "enantiomer". Compounds that are stereoisomers of one another, but are not enantiomers of one another, are called diastereoisomers. The terms "racemate" or "racemic mixture" refer to a mixture of equal parts of enantiomers. The term "chiral center" refers to a carbon atom to which four different groups are attached. The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E1 - E2}{E1 + E2} * 100$$

wherein E1 is the amount of the first enantiomer and E2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 50:30 is achieved, the ee with respect to the first enantiomer is 25%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. According to one embodiment of the invention, an ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred.

Enantiomeric enrichment is determined by one of ordinary skill in the art using standard techniques and procedures, such as high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is within the knowledge of one of ordinary skill in the art. In addition, the enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as

those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981. Examples of resolutions include recrystallization techniques or chiral chromatography.

Diastereoisomers differ in both physical properties and chemical reactivity. A mixture of diastereomers can be separated into enantiomeric pairs based on solubility, fractional crystallization or chromatographic properties, e.g., thin layer chromatography, column chromatography or HPLC.

Purification of complex mixtures of diastereomers into enantiomers typically requires two steps. In a first step, the mixture of diastereomers is resolved into enantiomeric pairs, as described above. In a second step, enantiomeric pairs are further purified into compositions enriched for one or the other enantiomer or, more preferably resolved into composition comprising pure enantiomers. Resolution of enantiomers typically requires reaction or molecular interaction with a chiral agent, e.g., a solvent or column matrix. Resolution of enantiomers may be achieved, for example, by converting the mixture of enantiomers, e.g., a racemic mixture, into a mixture of diastereomers by reaction with a pure enantiomer of a second agent, i.e., a resolving agent. The two resulting diastereomeric products can then be separated. The separated diastereomers are then reconverted to the pure enantiomers by reversing the initial chemical transformation.

Resolution of enantiomers can also be accomplished by differences in their non-covalent binding to a chiral substance, e.g., by chromatography on homochiral adsorbants. The noncovalent binding between enantiomers and the chromatographic adsorbant establishes diastereomeric complexes, leading to differential partitioning in the mobile and bound states in the chromatographic system. The two enantiomers therefore move through the chromatographic system, e.g, column, at different rates, allowing for their separation.

Chiral resolving columns are well known in the art and are commercially available (e.g., from MetaChem Technologies Inc., a division of ANSYS Technologies, Inc., Lake Forest, CA). Enantiomers can be analyzed and purified, for example, using chiral stationary phases (CSPs) for HPLC. Chiral HPLC columns typically contain one form of an enantiomeric compound immobilized to the surface of a silica packing material. For chiral resolution to occur, there must be at least three points of simultaneous interaction between the CSP and one analyte enantiomer, with one or more of these interactions being stereochemically dependent.

D-phenylglycine and L-leucine are Type I CSPs and use combinations of p-p

interactions, hydrogen bonds, dipole-dipole interactions, and steric interactions to achieve chiral recognition. To be resolved on a Type I column, analyte enantiomers must contain functionality complementary to that of the CSP so that the analyte undergoes essential interactions with the CSP. The sample should preferably contain one of the following functional groups: p-acid or p-base, hydrogen bond donor and/or acceptor, or an amide dipole. Derivatization is sometimes used to add the interactive sites to those compounds lacking them. The most common derivatives involve the formation of amides from amines and carboxylic acids.

The MetaChiral ODM™ is a type II CSP. The primary mechanisms for the formation of solute-CSP complexes is through attractive interactions, but inclusion complexes also play an important role. Hydrogen bonding, pi-pi, and dipole stacking are important for chiral resolution on the MetaChiral™ ODM. Derivatization is often necessary when the solute molecule does not contain the groups required for solute-column interactions. Derivatization, usually to benzylamides, is also required of some strongly polar molecules like amines and carboxylic acids, which would otherwise interact too strongly with the stationary phase through non-stereo-specific interactions.

The invention provides compounds of formula I as set forth above.

In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formula disclosed in US 6436964.

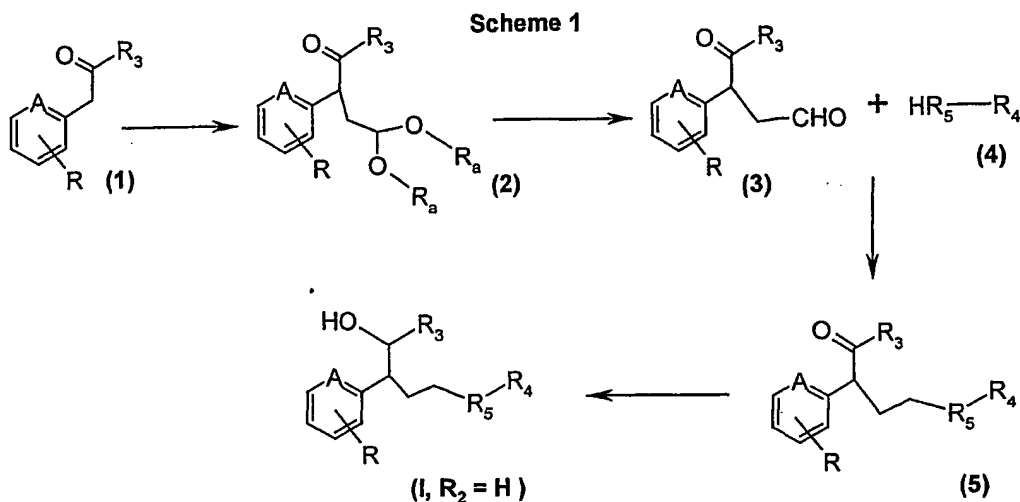
In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formula disclosed in US 5585374.

In certain embodiments, formula I set forth above may include a proviso that excludes compounds represented by the generic formulas disclosed in both US 6436964 and US 5585374.

Compounds of formula I can be separated into diastereomeric pairs by, for example, by separation by TLC. These diastereomeric pairs are referred to herein as diastereoisomer with upper TLC R_f; and diastereoisomer with lower TLC R_f. The diastereoisomers can further be enriched for a particular enantiomer or resolved into a single enantiomer using methods well known in the art, such as those described herein.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

The compounds of the invention are generally prepared according to the following schemes:



Group R is the same as $(R + R_1)$ as given in the general formula I. A, R_2 , R_3 , R_4 and R_5 have the same meanings as given in the general formula I and R_a is a lower alkyl group.

Starting material (1) is treated with a base, preferably potassium tert-butoxide, followed by alkylation with 2-bromoacetaldehyde dialkyl acetal or other carbonyl protected 2-haloacetaldehyde (e.g., the R_a alkyl groups can also be joined in a cycle to give a dioxolane or dioxane ring). Other alternative and appropriate bases to carry out the condensation include lithium amides, sodium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, cesium carbonate and the like with the aid or not of phase transfer catalysts. The reaction is preferably carried out in a solvent such as dimethyl sulfoxide or toluene at a temperature of 0°C to reflux.

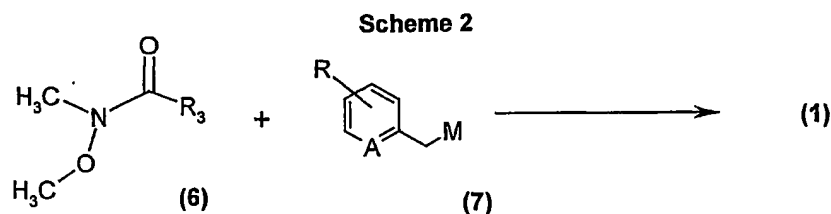
The use of 3-bromopropionaldehyde dialkyl acetal or other carbonyl protected 3-halopropionaldehyde allow to obtain, by following the same reaction conditions described above in Scheme 1, compound I having $m = 2$ as foreseen in the general formula.

Treatment of (2) with an acid, such as hydrochloric acid or p-toluenesulfonic acid or trifluoroacetic acid in a suitable organic solvent, achieves aldehyde (3). Generally, the reaction is conducted in a protic solvent, such a mixture of aqueous acid and acetone or tetrahydrofuran, at temperatures of 5°C to 75°C , preferably at ambient temperature. A preferred similar method consists of carrying out the reaction in a mixture of aqueous trifluoroacetic acid in a chlorinated solvent at r.t.

Aldehyde (3) is coupled with the desired amine (4) by reductive amination procedure to prepare (5). The reaction is preferably carried out at ambient temperature in

a chlorinated solvent such as dichloroethane or methylene chloride or chloroform in the presence of sodium triacetoxyborohydride and is substantially complete in one to 24 hours (see for example A. F. Abdel-Magid et al., *J. Org. Chem.*, **61**, 3849 (1996)) or can be carried out in a protic solvent (e.g., methanol) with the aid of sodium cyanoborohydride, optionally in the presence of molecular sieves.

Reduction of (5) to the alcohol (I) is readily accomplished using a reducing agent such as sodium borohydride or diisobutylaluminum hydride or other aluminum or boron hydride or other reduction method to carry out the conversion ketone to alcohol, well known to those skilled in the art, to prepare the hydroxy compound (I). The reaction is preferably carried out in an organic solvent such as methanol or methylene chloride or tetrahydrofuran at temperatures of -20°C to 0°C - ambient temperature.



Starting material (1) is either commercially available or can be prepared by coupling the appropriate Weinreb amide (6) (See Nahm et al., *Tetrahedron Lett.*, **22**, 3815, (1981)) with (7), as described in Scheme 2 above, where M is a metallic salt, such as lithium or magnesium halide. The reaction is preferably carried out under nitrogen atmosphere, in an aprotic solvent, such as tetrahydrofuran, at ambient or lower temperatures down to -78°C.

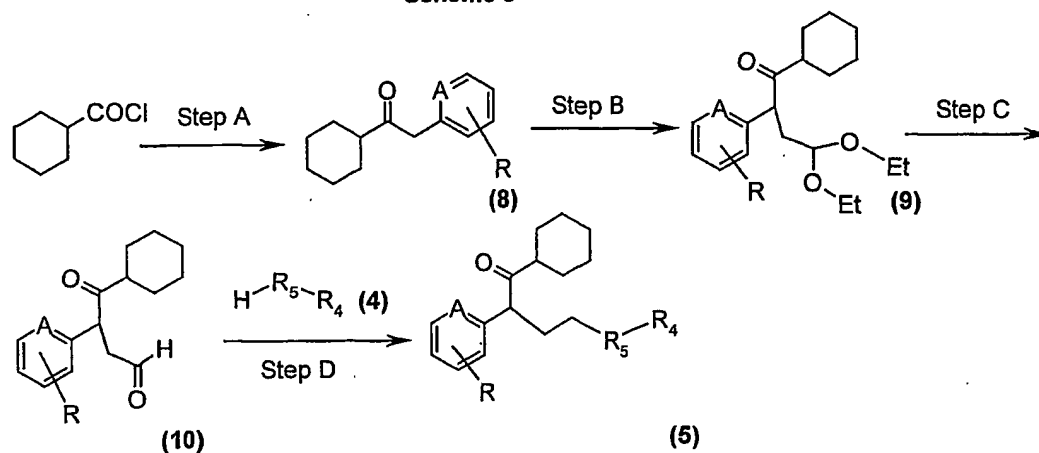
Alternatively, an ester of structure $\text{R}_3\text{COOalkyl}$ can be treated with a substituted benzylmagnesium chloride or benzylmagnesium bromide or lithium derivative under standard conditions well known in the art to provide the ketone of structure (1).

An alternative route to obtain compounds (1) consists of reacting the appropriate arylaldehyde with an alkylnitro derivative in a nitroaldol fashion, dehydration of the nitro alcohol thus obtained, followed by double bond reduction afford a 2-nitro(2-Ak)phenethyl derivative, which can undergo Nef reaction to yield the wished keto derivative 1. This kind of pathway is well documented in the experimental part and in the literature.

A preferred similar way of synthesis of (1) is the palladium catalysed coupling of an acyl halide with a compound (7) where M is Zn halide. More specifically, the compounds of formula (5) can be prepared following the procedure described in Scheme

3. All substituents, unless otherwise indicated, are as defined previously. The reagents and starting materials are readily available to one of ordinary skill in the art.

Scheme 3



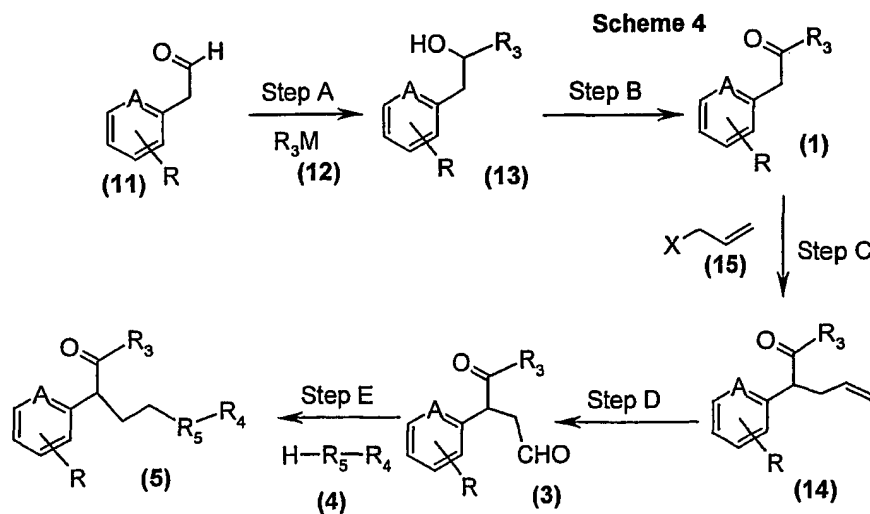
In Scheme 3, step A, for example, cyclohexanecarbonyl chloride is added to a mixture of the suitable benzylzinc chloride(bromide) and an appropriate palladium catalyst, e.g., dichlorobis(triphenylphosphine)palladium (II) stirred at 0°C in a solvent such as tetrahydrofuran. Afterwards, stirring is continued at r.t. for 4-24 h. Then the reaction is quenched for example with an aqueous saturated solution of ammonium chloride. Typical work-up procedure by extraction provides the ketone (8). Ketone (8) can be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane to provide the purified material. Alternatively, the crude ketone (8) can be used in step B without purification.

In Scheme 3, step B, ketone (8) is alkylated with bromoacetaldehyde diethyl acetal under conditions well known in the art to provide compound of structure (9). For example, ketone (8) is dissolved in a suitable organic solvent, such as dimethyl sulfoxide or toluene and treated with a slight excess of a suitable base, such as potassium tert-butoxide. The reaction is stirred for about 15 to 30 minutes at a temperature of between 0°C and the reflux temp. of the solvent and bromoacetaldehyde diethyl acetal is added dropwise to the reaction. One of ordinary skill in the art would readily appreciate that bromoacetaldehyde dimethyl acetal, bromoacetaldehyde ethylene acetal and the like may be used in place of the corresponding diethyl acetal.

In Scheme 3, step C, compound (9) is hydrolyzed under acidic conditions to provide aldehyde (10) in a manner analogous to the procedure described in Scheme 1. More specifically, for example, compound (9) is dissolved in a suitable organic solvent,

such as dichloromethane and treated with a suitable acid, such as aq. trifluoroacetic acid. The reaction mixture is stirred for about 1 to 6 hours at room temperature. The reaction mixture is then diluted with the same solvent, washed with brine; the organic layer is separated, dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to provide aldehyde (10). Aldehyde (10) can be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane. Alternatively, crude aldehyde (10) can be used directly in step D.

In Scheme 3, step D, aldehyde (10) is reductively aminated, under conditions well known in the art, with amine (4) to provide the ketone (5) in a manner analogous to the procedure described in Scheme 1. More specifically, for example, aldehyde (10) is dissolved in a suitable organic solvent, such as methylene chloride. To this solution is added about 1.05 or more equivalents of amine (4). Acetic acid may optionally be added to aid in dissolution of the amine (4). Then about 1.4 to 1.5 equivalents of sodium triacetoxyborohydride is added and the reaction is stirred at room temperature for about 3 to 5 hours. The reaction is then quenched by addition of a suitable base, such as aqueous sodium carbonate or hydroxide to provide a pH from 8 to about 12. The quenched reaction is then extracted with a suitable organic solvent, such as methylene chloride. The organic extracts are combined, washed with brine, dried, filtered and concentrated under vacuum to provide the compound of formula (5). This material can then be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/petroleum ether or hexane.



Alternatively, compounds of structure (5) can be prepared following the procedure described in Scheme 4. All substituents, unless otherwise indicated, are previously

defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

In Scheme 4, step A, aldehyde (11) is combined with a suitable organometallic reagent (12) under conditions well known in the art to provide alcohol (13). Examples of suitable organometallic reagents include Grignard Reagents, alkyl lithium reagents, alkyl zinc reagents, and the like. Grignard Reagents are preferred. For examples of typical Grignard Reagents and reaction conditions, see J. March, *"Advanced Organic Chemistry: Reactions, Mechanisms, and Structure"*, 2nd Edition, McGraw-Hill, pages 836-841 (1977). More specifically, aldehyde (11) is dissolved in a suitable organic solvent, such as tetrahydrofuran or toluene, cooled to about -5°C and treated with about 1.1 to 1.2 equivalents of a Grignard reagent of formula (12) wherein M is MgCl or MgBr. The reaction is stirred for about 0.5 to 6 hours, then quenched, and alcohol (13) is isolated by well-known work-up procedure.

In Scheme 4, step B, alcohol (13) is oxidized under standard conditions well known in the art, such as those described by J. March, *"Advanced Organic Chemistry: Reactions, Mechanisms, and Structure"*, 2nd Edition, McGraw-Hill, pages 1082-1084 (1977), to provide ketone (1). (Ketone (1) is the starting material used in Scheme 1 above.)

For example, the above oxidation is also performed using standard Swern Oxidation conditions which are well known to one of ordinary skill in the art, or the alcohol (13) is dissolved in a suitable organic solvent, such as methylene chloride, the solution cooled with a wet ice-acetone bath, and treated with 2.5 to 3.0 equivalents of dimethyl sulfoxide. After stirring for about 30 minutes, the reaction is then treated with about 1.8 equivalents of P_2O_5 . The reaction is stirred for about 3 hours and then, preferably, treated over about 30 minutes with about 3.5 equivalents of a suitable amine, such as triethylamine. The cooling bath is then removed and the reaction is stirred for about 8 to 16 hours. The ketone (1) is then isolated by standard extraction techniques well known in the art.

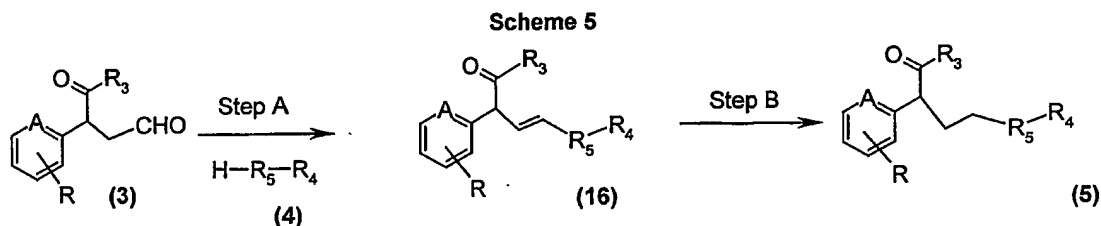
In Scheme 4, step C, ketone (1) is treated with a suitable base followed by addition of the alkene (15), wherein X is a suitable leaving group, to provide compound (14). For example, ketone (1) is combined with an excess of alkene (15) in a suitable organic solvent, such as tetrahydrofuran, and cooled with a wet ice acetone bath. Examples of suitable leaving groups are Cl, Br, I, tosylate, mesylate, and the like. Preferred leaving groups are Cl and Br. About 1.1 equivalents of a suitable base are added and the reaction is allowed to stir for about 2 hours at room temperature. Examples of

suitable bases are potassium tert-butoxide, sodium hydride, $\text{NaN}(\text{Si}(\text{CH}_3)_3)_2$, LDA, $\text{KN}(\text{Si}(\text{CH}_3)_3)_2$, NaNH_2 , sodium ethoxide, sodium methoxide and the like. Potassium tert-butoxide is the preferred suitable base. The reaction is then quenched with aqueous acid and compound (14) is isolated by usual work-up procedure.

In Scheme 4, step D, compound (14) is treated with a suitable oxidizing agent to provide aldehyde (3). (Aldehyde (3) is also prepared in Scheme 1.) Examples of suitable oxidizing agents are ozone, NaIO_4 /Osmium catalyst, and the like. Ozone is the preferred oxidizing agent. Examples of suitable oxidizing reagents and conditions are described by J. March, "*Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*", 2nd Edition, McGraw-Hill, pages 1090-1096 (1977).

For example, compound (14) is dissolved in a suitable organic solvent, such as methanol, a small amount of Sudan III is added, and the solution is cooled to about -20°C . Ozone is bubbled into the solution for about 4 hours until the pink color turns to a pale yellow color. Then a reducing agent such as Me_2S or tributylphosphine is added. Concentration provides the intermediate dimethyl acetal of aldehyde (3). This dimethyl acetal is readily hydrolyzed under standard acidic conditions to provide aldehyde (3). Alternatively, direct acidic work-up of the crude reaction mixture provides aldehyde (3). Alternatively, aldehyde (3) can be obtained directly by ozonolysis of (14) in a non-acetal forming solvent, such as methylene chloride.

In Scheme 4, step E, aldehyde (3) is reductively aminated under conditions analogous to those described above in Scheme 3, step D, to provide compound (5). (Compound 5 is also prepared in Scheme 1.)



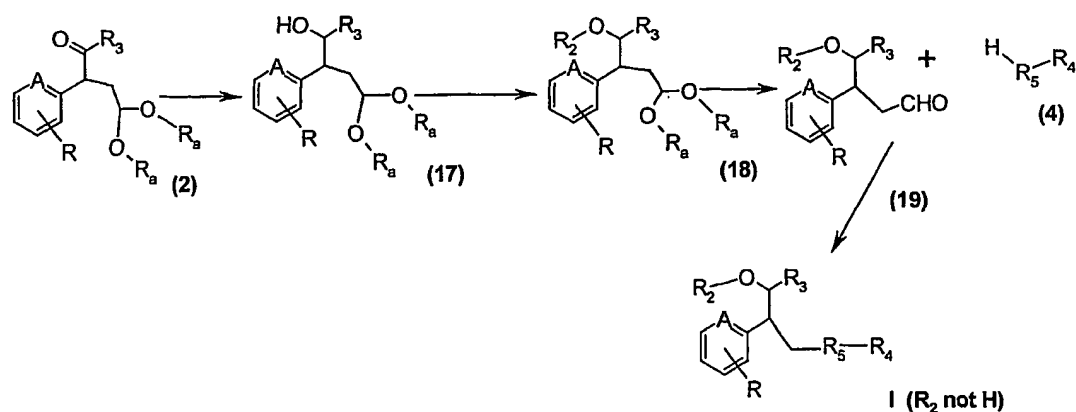
Scheme 5 provides an alternative synthesis for the preparation of ketone (5). All substituents, unless otherwise indicated, are previously defined. The reagents and starting materials are readily available to one of ordinary skill in the art.

In Scheme 5, step A, aldehyde (3) is condensed with amine (4) under standard conditions well known in the art to provide the enamine (16). For example, about 1.05 equivalents of aldehyde (3) dissolved in a suitable organic solvent, such as isopropyl

acetate or isopropanol, is added to neat amine (4), free base. Additional organic solvent is added to produce a slurry and the reaction is stirred for about 1 to 2 hours. The enamine (16) is then isolated by standard techniques, such as collection by filtration.

In Scheme 5, step B, the enamine (16) is hydrogenated under conditions well known to one of ordinary skill in the art to provide compound (5). For example, enamine (16) is combined with a suitable organic solvent, such as isopropyl alcohol and a catalytic amount of 5% palladium on carbon in a Parr bottle. The mixture is placed under 50 psi of hydrogen and shaken for about 2 days at room temperature. The slurry is then filtered to remove catalyst and the filtrate is concentrated to provide compound (5).

Scheme 6

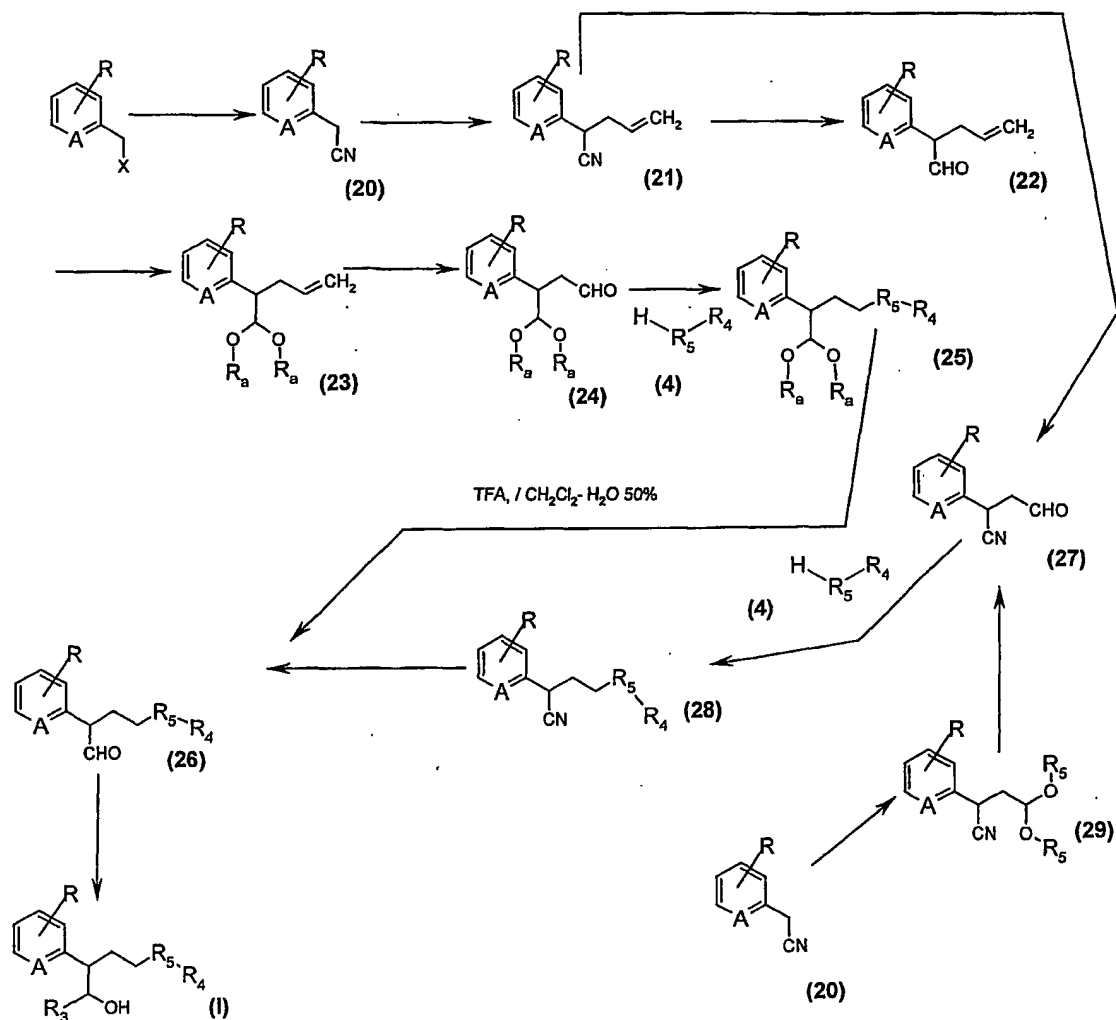


For the synthesis of compounds I where R_2 is different than H, the method given in Scheme 6 is used. Intermediate ketone (2) is reduced with the same reduction methods used above in scheme 1 for compound (5) affording intermediate (17), which is etherified by reaction with a base, for example NaH or potassium tert-butoxide or NaNH_2 or LiNH_2 or others in a suitable solvent e.g. tetrahydrofuran, affording the alkoxide, which is then reacted in situ with the appropriate $R_2\text{-X}$ with X leaving group (halogen or mesylate or tosylate) at a temperature of from 0°C to the reflux temperature. The so obtained compounds (18) can undergo the same reactions described in scheme 1 affording product I with R_2 is not H.

Alternatively, compounds of formula I where R_2 is not a hydrogen atom, can be obtained by alkylating compounds of formula I where $R_2 = \text{H}$ with the same methods described above for alkylating compound 17, limiting this procedure to the alkylation with very reactive halogenide or mesylate/tosylate (e.g., benzyl bromides) which can react under time/temperature controlled reaction condition, preferably at r.t.

Scheme 7 describes a double functionalization approach to the synthesis of Compound (I). This kind of approach can be useful for the synthesis of libraries of compounds (I) introducing different amine moieties and different R_3 groups at the same time.

Scheme 7



In scheme 7 R_a is a lower alkyl group or the two R_a groups are linked forming a 1,3-dioxolanyl or 1,3-dioxanyl group. An appropriate commercial benzyl derivative (with X = halogen or methanesulphonyloxy or p-toluenesulphonyloxy groups) can be reacted, as very well known to those skilled in the art, to afford the benzyl cyanide (20). These reactants can be converted following known alkylation methods into compounds

(21) or (27) respectively reacting them with allyl halogenides (or allyl mesylates or tosylates) or haloalkylaldehydes in their carbonyl protected form (acetals or dioxolanyl derivatives or other).

These alkylation reactions can be carried out by the use of bases to generate the reactive benzyl carbanions. Example of used bases are lithium diisopropylamide (LDA) or tert-Butyl lithium or NaH or potassium tert-butoxide or sodium amide or potassium amide or others in an appropriate solvent such as THF or Et₂O or DMF or other at a temperature ranging from -78°C to the reflux temperature. A preferred method of alkylation include the use of hindered bases such as LDA in the presence of hexamethyl phosphorous triamide or DMPU at -78°C - r.t.

Compounds (21) can be in turn reduced by the use of diisobutylaluminum hydride (DIBAL-H) in an appropriate solvent (toluene, DMF, CH₂Cl₂ or other) at a temperature ranging from -78°C to the reflux of the solvent. The so obtained aldehydes (22) are then carbonyl protected following methods very well known to those skilled in the art to give compounds (23), which can be catalytically osmiliated (C. P. Forbes *J.C.S. Perkin Trans I* 1979, 906-910) or undergo ozonolysis to afford compounds (24). Compounds (24) can be reductively aminated as described above to afford compounds (25). Deprotection by common methods leads to the aldehydes (26).

Compounds (26) can be alternatively obtained from compounds (21) applying the osmiliation or ozonolysis procedure on them. The so obtained cyanopropionaldehydes (27) are then reductively aminated to compound (28). Repeating the DIBAL-H reduction described above on these compounds affords the aldehydes (26).

Compounds (27) are also easily obtained from compounds (29) by simple deprotection of the carbonyl functionality. The reaction of R₃-M (where M is a metallic salt, such as lithium or magnesium halide) with compounds (26) afford compounds (I). A large number of organometallics such as lithium or magnesium derivatives are commercially available or easily prepared and can be reacted in an appropriate solvent such as THF or Et₂O or others at -78°C - reflux.

Stereochemistry

In Schemes 1, 6 and 7 compounds I are obtained in syn/anti mixture of diastereoisomers with ratio depending on the reaction condition used. The diastereoisomers can be separated by usual techniques known to those skilled in the art

including fractional crystallization of the bases or their salts or chromatographic techniques such as LC or flash chromatography. For both the diastereoisomers, the (+) enantiomer of formula Ia can be separated from the (-) enantiomer using techniques and procedures well known in the art, such as that described by J. Jacques, et al., "*Enantiomers, Racemates, and Resolutions*", John Wiley and Sons, Inc., 1981. For example, chiral chromatography with a suitable organic solvent, such as ethanol/acetonitrile and Chiralpak AD packing, 20 micron can also be utilized to effect separation of the enantiomers.

The free bases of formula I, their diastereoisomers or enantiomers can be converted to the corresponding pharmaceutically acceptable salts under standard conditions well known in the art. For example, the free base of formula I is dissolved in a suitable organic solvent, such as methanol, treated with one equivalent of maleic or oxalic acid for example, one or two equivalents of hydrochloric acid or methanesulphonic acid for example, and then concentrated under vacuum to provide the corresponding pharmaceutically acceptable salt. The residue can then be purified by recrystallization from a suitable organic solvent or organic solvent mixture, such as methanol/diethyl ether.

Combination treatments

In certain embodiments, disorders of the urinary tract are treated by administering a compound of formula I in combination with an additional 5-HT_{1A} antagonist or an antagonist of one or more additional class of receptors. In preferred embodiments a compound of formula I is administered in combination with an antagonist of an α 1-adrenergic, or muscarinic receptor.

In further embodiments, lower urinary tract disease is treated by administering a compound of formula I in combination with one or more inhibitor of the cyclooxygenase enzyme, which may inhibit both COX1 and COX2 isozymes or which may, alternatively, be selective for COX2 isozyme, and NO donor derivatives thereof.

Examples of antimuscarinic drugs for administration in combination with a compound of formula I are oxybutynin, tolterodine, darifenacin, and temiverine.

A compound of formula I may be administered in combination with α 1-adrenergic antagonists, for the therapy of lower urinary tract symptoms, whether or not these are associated with BPH. Preferred α 1-adrenergic antagonists suitable for administration in combination with a compound of formula I are, for example, prazosin, doxazosin,

terazosin, alfuzosin, and tamsulosin. Additional α 1-adrenergic antagonists suitable for administration in combination with a compound of formula I are described in U.S. Patents No. 5,798,362, 5,990,114; 6,306,861; 6,365,591; 6,387,909; and 6,403,594.

Examples of 5-HT_{1A} antagonists that may be administered in combination with a compound of formula I are found in Leonardi et al., *J. Pharmacol. Exp. Ther.* **299**: 1027-1037, 2001 (e.g., Rec 15/3079), U.S. Patent No. 6,071,920, other phenylpiperazine derivatives described in WO 99/06383 and pending U.S. Patent Applications Serial No. 10/266,088 and 10/266,104 filed on October 7, 2002. Additional 5-HT_{1A} antagonists include DU-125530 and related compounds described in U.S. Patent No. 5,462,942 and robalzotan and related compounds described in WO 95/11891.

Examples of selective COX2 inhibitors that may be administered in combination with a compound of formula I are, without limitation, nimesulide, meloxicam, rofecoxib, celecoxib, parecoxib and valdecoxib. Additional examples of selective COX2 inhibitors are described, without limitation, in US 6,440,963. Examples of non-selective COX1-COX2 inhibitors are, without limitation, acetylsalicylic acid, niflumic acid, flufenamic acid, enfenamic acid, meclofenamic acid, tolfenamic acid, thiaprophenic acid, ibuprofen, naproxen, ketoprofen, flurbiprofen, furprofen, indomethacin, acemethacin, proglumethacin, ketorolac, diclofenac, etodolac, sulindac, fentiazac, tenoxicam, lornoxicam, cynnoxicam, ibuproxam, nabumetone, tolmetin, amtolmetin. Accordingly, each of the foregoing are non-limiting examples of COX inhibitors that may be administered in combination with a compound of formula I.

Examples of derivatives of COX inhibitors that may be administered in combination with a compound of formula I are derivatives of COX inhibitors bearing nitrate (nitrooxy) or nitrite groups, such as those given, for example, in WO 98/09948, able to release NO in vivo.

Pharmaceutical Compositions

The invention further provides pharmaceutical compositions comprising a compound of formula I or an enantiomer, diastereomer, N-oxide, crystalline form, hydrate, solvate, active metabolite or pharmaceutically acceptable salt of the compound. The pharmaceutical composition may also include optional additives, such as a pharmaceutically acceptable carrier or diluent, a flavouring, a sweetener, a preservative, a dye, a binder, a suspending agent, a dispersing agent, a colorant, a disintegrator, an excipient, a diluent, a lubricant, an absorption enhancer, a bactericide and the like, a

stabiliser, a plasticizer, an edible oil, or any combination of two or more of said additives.

Suitable pharmaceutically acceptable carriers or diluents include, but are not limited to, ethanol, water, glycerol, aloe vera gel, allantoin, glycerine, vitamin-A and E oils, mineral oil, phosphate buffered saline, PPG2 myristyl propionate, magnesium carbonate, potassium phosphate, vegetable oil, animal oil and solketal.

Suitable binders include, but are not limited to, starch, gelatine, natural sugars such as glucose, sucrose and lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, vegetable gum, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Suitable disintegrators include, but are not limited to, starch such as corn starch, methyl cellulose, agar, bentonite, xanthan gum and the like.

Suitable lubricants include, but are not limited to, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Suitable suspending agents include, but are not limited to, bentonite.

Suitable dispersing and suspending agents include, but are not limited to, synthetic and natural gums such as vegetable gum, tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone and gelatine.

Suitable edible oils include, but are not limited to, cottonseed oil, sesame oil, coconut oil and peanut oil.

Examples of additional additives include, but are not limited to, sorbitol, talc, stearic acid and dicalcium phosphate.

Unit Dosage Forms

The pharmaceutical composition may be formulated as unit dosage forms, such as tablets, pills, capsules, boluses, powders, granules, sterile parenteral solutions, sterile parenteral suspensions, sterile parenteral emulsions, elixirs, tinctures, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories. The unit dosage forms may be used for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation, transdermal patches, and a lyophilized composition. In general, any delivery of active ingredients that results in systemic availability of such ingredients can be used. Preferably the unit dosage form is an oral dosage form, most preferably a solid oral dosage; therefore the preferred dosage forms are tablets, pills and capsules. However, parenteral preparations are preferred too.

Solid unit dosage forms may be prepared by mixing the active agents of the present invention with a pharmaceutically acceptable carrier and any other desired

additives as described above. The mixture is typically mixed until a homogeneous mixture of the active agents of the present invention is obtained and the carrier and any other desired additives are formed, i.e. the active agents are dispersed evenly throughout the composition. In this case, the composition can be formed as dry or moist granules.

Dosage forms can be formulated as, for example, "immediate release" dosage forms. "Immediate release" dosage forms are typically formulated as tablets that release at least 60%-90% of the active ingredient within 30-60 min when tested in a drug dissolution test, e.g., U.S. Pharmacopeia standard <711>. In a preferred embodiment, immediate dosage forms release at 75% of active ingredient within about 45 min.

Dosage forms can also be formulated as, for example, "controlled release" dosage forms. "Controlled," "sustained," "extended" or "time release" dosage forms are equivalent terms that describe the type of active agent delivery that occurs when the active agent is released from a delivery vehicle at an ascertainable and manipulatable rate over a period of time, which is generally on the order of minutes, hours or days, typically ranging from about sixty minutes to about 3 days, rather than being dispersed immediately upon entry into the digestive tract or upon contact with gastric fluid. A controlled release rate can vary as a function of a multiplicity of factors. Factors influencing the rate of delivery in controlled release include the particle size, composition, porosity, charge structure, and degree of hydration of the delivery vehicle and the active ingredient(s), the acidity of the environment (either internal or external to the delivery vehicle), and the solubility of the active agent in the physiological environment, i.e., the particular location along the digestive tract. Typical parameters for dissolution test of controlled release forms are found in U.S. Pharmacopeia standard <724>.

Dosage forms can also be formulated to deliver active agent in multiphasic stages whereby a first fraction of an active ingredient is released at a first rate and at least a second fractions of active ingredient is released at a second rate. In a preferred embodiment, a dosage form can be formulated to deliver active agent in a biphasic manner, comprising a first "immediate release phase", wherein a fraction of active ingredient is delivered at a rate set forth above for immediate release dosage forms, and a second "controlled release phase," wherein the remainder of the active ingredient is released in a controlled release manner, as set forth above for controlled release dosage forms.

Tablets or pills can be coated or otherwise prepared so as to form a unit dosage

form that has delayed and/or sustained action, such as controlled release and delayed release unit dosage forms. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of a layer or envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release.

Biodegradable polymers for controlling the release of the active agents include, but are not limited to, polylactic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and crosslinked or amphipathic block copolymers of hydrogels.

For liquid dosage forms, the active substances or their physiologically acceptable salts are dissolved, suspended or emulsified, optionally with the usually employed substances such as solubilizers, emulsifiers or other auxiliaries. Solvents for the active combinations and the corresponding physiologically acceptable salts can include water, physiological salt solutions or alcohols, e.g. ethanol, propanediol or glycerol. Additionally, sugar solutions such as glucose or mannitol solutions may be used. A mixture of the various solvents mentioned may be used in the present invention too.

A transdermal dosage form is contemplated by the present invention too. Transdermal forms may be a diffusion transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Other transdermal dosage forms include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery systems. Transdermal dosage forms may be used for delayed release and sustained release of the active agents of the present invention.

The pharmaceutical compositions and unit dosage forms of the present invention for parenteral administration, and in particular by injection, typically include a pharmaceutically acceptable carrier, as described above. A preferred liquid carrier is vegetable oil. Injection may be, for example, intravenous, epidural, intrathecal, intramuscular, intraluminal, intratracheal or subcutaneous.

The active agents can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The active agents of the present invention may also be coupled with soluble

polymers such as targetable drug carriers. Such polymers include, but are not limited to, polyvinylpyrrolidone, pyran copolymers, polyhydroxypropylmethacrylamidophenol, polyhydroxyethylaspartamidophenol, and polyethylenoxypolylysine substituted with palmitoyl residues.

Administration

The pharmaceutical composition or unit dosage forms of the present invention may be administered by a variety of routes, such as the oral and enteral, intravenous, intramuscular subcutaneous, transdermal, transmucosal (including rectal and buccal) and by inhalation routes. Oral or transdermal routes are preferred (e.g., solid or liquid formulations or skin patches, respectively).

The pharmaceutical composition or unit dosage forms comprising an effective amount of the present invention may be administered to an animal, preferably a human, in need of treatment of neuromuscular dysfunction of the lower urinary tract described by E. J. McGuire in "Campbell's UROLOGY", 5th Ed., 616-638, 1986, W.B. Saunders Company, and patients affected by any physiological dysfunction related to impairment of 5-HT_{1A} receptor function. Such dysfunctions include, without limitation, central-nervous-system disorders such as depression, anxiety, eating disorders, sexual dysfunction, addiction and related problems.

As used herein, the term "effective amount" refers to an amount that results in measurable amelioration of at least one symptom or parameter of a specific disorder. In a preferred embodiment, the compound treats disorders of the urinary tract, such as urinary urgency, overactive bladder, increased urinary frequency, reduced urinary compliance (reduced bladder storage capacity), cystitis (including interstitial cystitis), incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the bladder, or central nervous system disorders due to serotonergic dysfunction (such as anxiety, depression, hypertension, sleep/wake cycle disorders, feeding behaviour, sexual function and cognition disorders in mammals (particularly a human) associated to stroke, injury, dementia and due to neurological development, disorders from hyperactivity related to an attention deficit (ADHD), drug addiction, drug withdrawal, irritable bowel syndrome.

The pharmaceutical composition or unit dosage form of the present invention may be administered according to a dosage and administration regimen defined by routine testing in the light of the guidelines given above in order to obtain optimal activity while minimising toxicity or side effects for a particular patient. However, such fine tuning of the therapeutic regimen is routine in the light of the guidelines given herein.

The dosage of the active agents of the present invention may vary according to a variety of factors such as underlying disease conditions, the individual's condition, weight, sex and age, and the mode of administration. An effective amount for treating a disorder can easily be determined by empirical methods known to those of ordinary skill in the art, for example by establishing a matrix of dosages and frequencies of administration and comparing a group of experimental units or subjects at each point in the matrix. The exact amount to be administered to a patient will vary depending on the state and severity of the disorder and the physical condition of the patient. A measurable amelioration of any symptom or parameter can be determined by a person skilled in the art or reported by the patient to the physician. It will be understood that any clinically or statistically significant attenuation or amelioration of any symptom or parameter of urinary tract disorders is within the scope of the invention. Clinically significant attenuation or amelioration means perceptible to the patient and/or to the physician.

For example, a single patient may suffer from several symptoms of dysuria simultaneously, such as, for example, urgency and excessive frequency of urination or both, and these may be reduced using the methods of the present invention. In the case of incontinence, any reduction in the frequency or volume of unwanted passage of urine is considered a beneficial effect of the present method of treatment.

The amount of the agent to be administered can range between about 0.01 and about 25 mg/kg/day, preferably between about 0.1 and about 10 mg/kg/day and most preferably between 0.2 and about 5 mg/kg/day. It will be understood that the pharmaceutical formulations of the present invention need not necessarily contain the entire amount of the agent that is effective in treating the disorder, as such effective amounts can be reached by administration of a plurality of doses of such pharmaceutical formulations.

In a preferred embodiment of the present invention, the compounds are formulated in capsules or tablets, preferably containing 50 to 200 mg of the compounds of the invention, and are preferably administered to a patient at a total daily dose of 50 to 400 mg, preferably 150 to 250 mg and most preferably about 200 mg, for relief of urinary incontinence and dysfunctions under treatment with 5-HT_{1A} receptor ligand.

A pharmaceutical composition for parenteral administration contains from about 0.01% to about 100% by weight of the active agents of the present invention, based upon 100% weight of total pharmaceutical composition.

Generally, transdermal dosage forms contain from about 0.01% to about 100% by

weight of the active agents versus 100% total weight of the dosage form.

The pharmaceutical composition or unit dosage form may be administered in a single daily dose, or the total daily dosage may be administered in divided doses. In addition, co-administration or sequential administration of another compound for the treatment of the disorder may be desirable. For example, the compounds of the invention may be administered in combination with more antimuscarinic, α_1 -adrenergic antagonist, 5-HT_{1A} receptor antagonist, or COX inhibitors or NO releasing derivatives thereof, for the therapy of lower urinary tract symptoms. Examples of antimuscarinics, α_1 -adrenergic antagonists, 5-HT_{1A} receptor antagonist, COX inhibitors and NO releasing derivatives thereof are set forth above, without limitation.

For combination treatment where the compounds are in separate dosage formulations, the compounds can be administered concurrently, or each can be administered at separate staggered times. For example, the compound of the invention may be administered in the morning and the antimuscarinic compound may be administered in the evening, or vice versa. Additional compounds may be administered at specific intervals too. The order of administration will depend upon a variety of factors including age, weight, sex and medical condition of the patient; the severity and aetiology of the disorders to be treated, the route of administration, the renal and hepatic function of the patient, the treatment history of the patient, and the responsiveness of the patient. Determination of the order of administration may be fine-tuned and such fine-tuning is routine in the light of the guidelines given herein.

Uses-Methods for Treatment

Without wishing to be bound by theory, it is believed that administration of 5-HT_{1A} receptor antagonists prevents unwanted activity of the sacral reflex and/or cortical mechanisms that control micturition. Thus, it is contemplated that a wide range of neuromuscular dysfunctions of the lower urinary tract can be treated using the compounds of the present invention, including without limitation dysuria, incontinence and enuresis (overactive bladder). Dysuria includes urinary frequency, nocturia, urgency, reduced urinary compliance (reduced bladder storage capacity), difficulty in emptying the bladder, i.e. a suboptimal volume of urine is expelled during micturition. Incontinence syndromes include stress incontinence, urgency incontinence and enuresis incontinence, as well as mixed forms of incontinence. Enuresis refers to the involuntary passage of urine at night or during sleep.

The compounds of the present invention may also be useful for the treatment of central nervous system disorders due to serotonergic dysfunction.

The following examples represent typical syntheses of the compounds of formula I as described generally above. These examples are illustrative only and are not intended to limit the invention in any way. The reagents and starting materials are readily available to one of ordinary skill in the art.

Example 1

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline

2-(2-Cyclohexyl-2-oxoethyl)-benzonitrile (Compound 1a)

To a solution of 0.47 g of 2-tolunitrile in 4 ml of THF was added 0.535 ml of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)pyrimidinone (DMPU) and the mixture was cooled at -78°C ; 2.22 ml of a 2M sol. of LDA in THF was then dropped during 5 min., then the reaction mixture was stirred at the same temperature for 15 min. followed by dropwise addition of 0.757 g of N-methyl-N-methoxycyclohexanecarboxamide in 4 ml of THF. After 1 h stirring at -78°C , the reaction mixture was quenched with a 10% aq. sol. of NH_4Cl . The temperature was allowed to rise at r.t. and the mixture was extracted with EtOAc (2x20ml), washed with 30 ml of brine, dried on Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash chromatography (PE – EtOAc 90:10) to afford 0.34 g of the title compound.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.10-2.05 (m, 10H); 2.45-2.60 (m, 1H); 4.00 (m, 2H); 7.20-7.43 (m, 2H); 7.48-7.70 (m, 2H);

3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutylaldehyde diethyl acetal (Compound 1b)

To a suspension of 414 mg of 60% NaH oil dispersion in 10 ml of anhydrous DMF was added drop wise during 6 min under a nitrogen stream, a solution of 1.84 g of compound 1a in 5 ml of DMF and the reaction mixture was stirred at r.t. for 1 h; then was added 2.15 g of 2-bromoacetaldehyde diethyl acetal (97 %) in 5 ml of DMF; the mixture was stirred at r.t. for 15', then at 80°C for 5.5 h. Afterwards, the mixture was diluted with H_2O (250 ml), acidified with 2 N HCl, extracted with Et_2O (3 x 50 ml), washed with H_2O (40 ml), dried (Na_2SO_4) and evaporated in vacuo, affording a crude (brownish oil), which was

purified by flash chromatography (PE - EtOAc 90:10) to yield 1.91 g of compound 1b as a yellowish oil.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.09-1.26 (m, 6H); 1.27-1.39 (m, 4H); 1.46-1.57 (m, 1H); 1.59-1.74 (m, 3H); 1.77-1.88 (m, 1H); 1.93-2.08 (m, 2H); 2.38-2.50 (m, 2H); 3.39-3.51 (m, 2H); 3.54-3.72 (m, 2H); 4.30-4.34 (m, 1H); 4.53-4.61 (m, 1H); 7.33-7.44 (m, 2H); 7.51-7.61 (m, 1H); 7.66-7.72 (m, 1H).

3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyraldehyde (Compound 1c)

A mixture of 1 g of the compound 1b, 9.5 ml of 50% aq. trifluoroacetic acid and 19 ml of CH_2Cl_2 was stirred for 2 h at r.t., then diluted with 8 ml of CH_2Cl_2 . The organic layer was separated, washed with brine (2 x 15 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo to afford a crude (0.788 g), used in the next step without further purification.

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.01-2.11 (m, 10H); 2.31-2.43 (m, 1H); 2.64 (dd, 1H); 3.29-3.41 (m, 1H); 4.78 (dd, 1H); 7.25-7.37 (m, 1H); 7.39-7.53 (m, 2H); 7.61-7.64 (m, 1H); 9.62-9.68 (m, 1H).

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline

A mixture of 0.197 g of the compound 1c, 0.177 g of 8-(N-methyl-2-aminoethoxy)-quinoline, 0.31 g of sodium triacetoxyborohydride, 0.17 ml of AcOH and 6 ml of CH_2Cl_2 was stirred at r.t. for 1 h and alkalised with 2 N NaOH. The organic layer was separated, washed with brine (2 x 15 ml), dried (Na_2SO_4) and evaporated to dryness in vacuo to give a crude which was purified by flash chromatography (CH_2Cl_2 - MeOH 95:5) affording the title compound (0.17 g; 52%).

$^1\text{H-NMR}$ (CDCl_3 , δ): 1.11-1.40 (m, 5H); 1.51-1.60 (m, 1H); 1.61-1.83 (m, 6H); 1.85-2.02 (m, 2H); 2.30-2.52 (m, 5H); 2.95-3.08 (m, 2H); 4.26-4.38 (m, 2H); 4.50-4.61 (m, 1H); 7.11 (d, 1H); 7.32-7.38 (m, 1H); 7.39-7.57 (m, 4H); 7.67 (d, 1H); 8.15 (d, 1H); 8.92-8.99 (m, 1H).

$[\text{M}+\text{H}]^+ = 456.25$

Example 2

8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-N-methyl-2-aminoethoxy}-quinoline

To a solution of 0.17 g of Compound of Example 1 in MeOH (5 ml), cooled at 0°C, 21.2 mg of NaBH₄ were added; the resulting mixture was stirred at 0°C for 30', then 1 h at r.t. Afterwards, the solvent was evaporated in vacuo and the crude poured into H₂O (10 ml) and extracted with CH₂Cl₂ (3x10 ml). The organic layer was separated, dried (Na₂SO₄) and evaporated to dryness in vacuo. The crude was purified by flash chromatography (EtOAc – 2 N methanolic ammonia 97:3) affording the title compound (55 mg; 32%).
[M+H]⁺ = 458.42

Example 3

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(2,6-dimethylphenyl)-piperidine

The title compound was obtained following the procedure described for the compound of Example 1, but using 4-(2,6-dimethylphenyl)-piperidine instead of 8-(N-methyl-2-aminoethoxy)-quinoline. Purification by flash chromatography (CH₂Cl₂ – MeOH 97:3) yielded the title compound (32.8%) as an oil.

¹H-NMR (CDCl₃, δ): 1.09-1.43 (m, 5H), 1.49-1.86 (m, 7H), 1.88-1.94 (m, 2H), 1.96-2.14 (m, 3H), 2.39-2.61 (m, 10H), 2.91-3.06 (m, 3H), 4.57-4.77 (m, 1H), 6.96-7.07 (m, 3H), 7.32-7.47 (m, 2H), 7.54-7.63 (m, 1H); 7.66-7.74 (m, 1H).

[M+H]⁺ = 443.33

Example 4

1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-4-(2,6-dimethylphenyl)-piperidine

The title compound was obtained following the procedure described for the compound of Example 2, but using the compound of Example 3 as starting material instead of the compound of Example 1. Purification by flash chromatography (CH₂Cl₂ - MeOH / NH₃ 97:3) yielded the title compound (20.9%) as an oil.

¹H-NMR (CDCl₃, δ): 1.09-1.43 (m, 5H), 1.49-1.86 (m, 7H), 1.88-1.94 (m, 2H), 1.96-2.14 (m, 3H), 2.39-2.61 (m, 10H), 2.91-3.06 (m, 3H), 4.57-4.77 (m, 1H), 6.96-7.07 (m, 3H), 7.32-7.47 (m, 2H), 7.54-7.63 (m, 1H); 7.66-7.74 (m, 1H).

[M+H]⁺ = 445.44

Example 5**1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(4-fluoro-2-methoxyphenoxy)-piperidine**

The title compound was obtained following the procedure described for the compound of Example 1, but using 4-(4-fluoro-2-methoxyphenoxy)-piperidine instead of 8-(N-methyl-2-aminoethoxy)-quinoline. Purification by flash chromatography (EP - EtOAc - MeOH / NH₃ 7:3:0.2) yielded the title compound (12.3%) as an oil.

¹H-NMR (CDCl₃, δ): 1.06-1.33 (m, 5H), 1.41-2.90 (m, 16H), 2.58-2.76 (m, 2H), 3.74 (s, 3H); 3.98-4.11 (m, 1H), 4.89-4.54 (m, 1H), 6.43-6.52 (m, 1H); 6.54-6.60 (m, 1H); 6.73-6.81 (m, 1H); 7.22-7.33 (m, 1H); 7.35-7.53 (m, 2H); 7.57-7.69 (m, 1H).

[M+H]⁺ = 479.29

Example 6 Radioligand binding to recombinant 5-HT_{1A} receptors**A. Method:**

A Genomic clone G-21 coding for the human 5HT_{1A}-serotonergic receptor is stably transfected in a human cell line (HeLa). HeLa cells are grown as monolayers in Dulbecco's modified Eagle medium (DMEM), containing 10% foetal bovine serum, gentamycin (0.1 mg/ml) and 5% carbon dioxide, at 37°C. The cells are detached from the growth flask at 95% confluence by a cell scraper and are lysed in cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4). The homogenates are centrifuged at 40000 x g x 20 minutes and the pellets are resuspended in a small volume of cold 5 mM Tris and 5 mM EDTA buffer (pH 7.4) and immediately frozen and stored at -70°C until use. On the day of experiment, the cell membranes are resuspended in incubation buffer: 50 mM Tris HCl (pH 7.4), 2.5 mM MgCl₂, 10 mM pargyline (Fargin et al., *Nature* **335**, 358-360, 1988). The membranes are incubated in a final volume of 1 ml for 30 minutes at 30°C with 1 nM [³H]8-OH-DPAT, in the absence or presence of the test compounds. Non-specific binding is determined in the presence of 10 μM 5-HT. Incubation is stopped by addition of cold Tris-HCl buffer and rapid filtration through a 0.2%-polyethyleneimine-pretreated Whatman-GF/B or Schleicher-&-Schuell-GF52 filter.

B. Results

The affinity of the tested compounds is evaluated as inhibition of specific binding

of the radioligand to 5-HT_{1A} receptors (IC₅₀) by using the non-linear curve-fitting program Allfit (De Lean et al., *Am. J. Physiol.* **235**, E97-E102 (1978)). The IC₅₀ value is converted to an affinity constant (K_i) by the equation of Cheng & Prusoff (Cheng Y. C., et al., *Biochem. Pharmacol.* **22**, 3099-3108 (1973)).

Example 7 Effects on rhythmic bladder-voiding contractions induced by bladder filling in anaesthetised rats

A. Method:

Female Sprague-Dawley rats weighing 225-275 g (CrI: CD[®] (SD) IGS BR, Charles River Italia) are used. The animals are housed with free access to food and water and maintained on a forced 12-hour alternating light-dark cycle at 22-24°C for at least one week, except during the experiment. The activity on rhythmic bladder voiding contractions is evaluated according to the method of Dray (Dray J., *Pharmacol. Methods*, **13**:157, 1985), with some modifications as in Guarneri (Guarneri, *Pharmacol. Res.* **27**:173, 1993). Briefly, the rats are anaesthetised by subcutaneous injection of 1.25 g/kg (5 ml/kg) urethane, after which the urinary bladder is catheterised via the urethra using PE 50 polyethylene tubing filled with physiological saline. The catheter is tied in place with a ligature around the external urethral orifice and is connected to conventional pressure transducers (Statham P23 ID/P23 XL). The intravesical pressure is displayed continuously on a chart recorder (Battaglia Rangoni KV 135 with DCI/TI amplifier). The bladder is then filled via the recording catheter by incremental volumes of warm (37°C) saline until reflex bladder-voiding contractions occurred (usually 0.8-1.5 ml). For intravenous injection of bioactive compounds, PE 50 polyethylene tubing filled with physiological saline is inserted into the jugular vein.

From the cystometrogram, the number of contractions recorded 15 minutes before (basal values) and after treatment, as well as the mean amplitude of these contractions (mean height of the peaks in mmHg), is evaluated.

Since most compounds produce an effect that is relatively rapid in onset and leads to a complete cessation of bladder contractions, bioactivity is conveniently estimated by measuring the duration of bladder quiescence (i.e., the length of the time during which no contractions occurred). The number of tested animals showing a reduction in the number of contractions higher than 30% of that observed in the basal period is also recorded.

To compare the potency of tested compounds for inhibiting the bladder voiding

contractions, equieffective doses which result in the disappearance of contractions for a time of 10 minutes (ED_{10min}) are computed by means of linear regression using the least square method. The extrapolated doses which induce a reduction in the number of contractions greater than 30% in 50% of the treated rats (ED_{50}) is evaluated by the method of Bliss (Bliss C. I., *Quart J. Pharm. Pharmacol.* **11**, 192-216, 1938).

B. Results

The rapid distension of the urinary bladder in urethane-anaesthetised rats produces a series of rhythmic bladder-voiding contractions whose characteristics have been described (Maggi et al., *Brain Res.* 380:83, 1986; Maggi et al., *J. Pharmacol. Exp. Ther.*, **230**: 500, 1984). The frequency of these contractions is related to the sensory afferent arm of reflex micturition and to the integrity of the micturition centre, while their amplitude depends on the function of the reflex efferent arm. In this model system, compounds that act mainly on the central nervous system (such as morphine) cause a block in voiding contractions, whereas drugs that act at the level of the detrusor muscle, such as oxybutynin, lower the amplitude of the bladder contractions.

Example 8 Effect on cystometric parameters in conscious rats after oral administration

A. Method:

Male Sprague-Dawley rats [CrI: CD[®] (SD) IGS BR] of 300-400 g supplied by Charles River Italia are used. The animals are housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature, except during the experiment. To quantify urodynamic parameters in conscious rats, cystometrographic studies is performed according to the procedure previously reported (Guarneri et al., *Pharmacol. Res.* **24**: 175, 1991).

Briefly, the rats are anaesthetised by intraperitoneal administration of 3 ml/kg of Equithensin solution (pentobarbital 30 mg/kg and chloral hydrate 125 mg/kg) and placed in a supine position. An approximately-10-mm-long midline incision is made in the shaved and cleaned abdominal wall. The urinary bladder is gently freed from adhering tissues, emptied and then cannulated via an incision in the bladder body, using a polyethylene cannula (0.58-mm internal diameter, 0.96-mm external diameter) which is permanently sutured with silk thread. The cannula is exteriorised through a subcutaneous

tunnel in the retroscapular area, where it is connected to a plastic adapter in order to avoid the risk of removal by the animal. For drug testing, the rats are utilised one day after implantation.

On the day of the experiment, rats are placed in modified Bollman cages, i.e., restraining cages, that are large enough to permit the rats to adopt a normal crouched posture, but narrow enough to prevent turning around. After a stabilisation period of about 20 minutes, the free tip of the bladder cannula is connected through a T-shaped tube to a pressure transducer (Statham P23XL) and to a peristaltic pump (Gilson minipuls 2) for continuous infusion of a warm (37°C) saline solution into the urinary bladder, at a constant rate of 0.1 ml/minute. The intraluminal-pressure signal during infusion of saline into the bladder is continuously recorded on a polygraph (Rectigraph-8K San-ei with BM614/2 amplifier from Biomedica Mangoni). The cystometrogram is used to evaluate the urodynamic parameters of bladder volume capacity (BVC) and micturition pressure (MP). BVC (ml) is defined as the volume of saline infused into the bladder necessary to induce detrusor contraction followed by micturition. MP (mmHg) is defined as the maximal intravesical pressure caused by contraction during micturition. Basal BVC and MP values are evaluated as mean of the values observed in the cystometrograms recorded in an initial period of 30-60 minutes. Following determination of basal BVC and MP, the infusion is interrupted and the test compounds are administered orally by a stomach tube. Bladder infusion is resumed and changes in BVC and MP are evaluated from the mean values obtained in the cystometrograms observed during 1, 2, 3, 4 and 5 hours after treatment. Compounds are administered in a volume of 2 ml/kg and groups of control animals receive the same amount of vehicle (0.5% methocel in water) orally.

Statistical analysis

Data are expressed as mean \pm standard error. The percent changes of BVC and MP *versus* the basal values, as well as Δ values (difference in ml or mmHg) of BVC and MP (BVC or MP at time "x" minus basal value), are evaluated for each rat/time. Data are reported as % changes *versus* basal values.

Statistical analysis on BVC and MP values, as well as on Δ values, is performed by S.A.S./STAT software, version 6.12. The observed differences between vehicle (control) and test treatments are evaluated on Δ values of BVC and MP, whereas the differences between the values at different times *versus* basal values are analyzed on

original BVC and MP data.

Example 9 Inhibition of stereotypy (rhythmic forepaw treading) induced by 8-OH-DPAT in rats (post-synaptic antagonism)

A. Method:

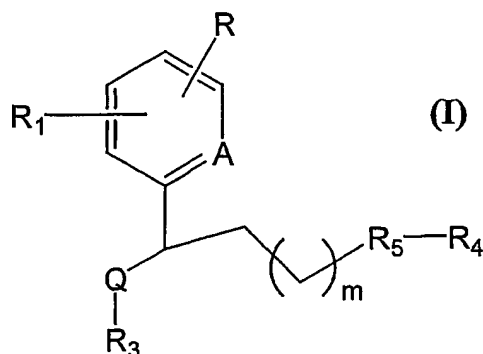
The inhibitory effect of 5-HT_{1A}-receptor antagonists on stereotyped forepaw treading induced in rats by subcutaneous injection of 8-OH-DPAT is evaluated by the method of Tricklebank (Tricklebank et al., *Eur. J. Pharmacol.*, **117**: 15, 1985) with minor modifications as described below.

Male Sprague-Dawley rats [CrI: CD[®] (SD) IGS BR] weighing 150-175 g from Charles River Italia are used. The animals are housed with free access to food and water and maintained on a forced 12-hour-light/12-hour-dark cycle at 22-24°C of temperature. On the day of the experiment, the rats are placed singly in clear plastic containers, 10-15 minutes before administration of the vehicle or compounds to be tested. For evaluation of antagonistic activity after oral administration, the compounds are administered 1 and 4 hours before induction of stereotypy by 8-OH-DPAT (1 mg/kg subcutaneously). Observation sessions last 30 seconds and begin 3 min after 8-OH-DPAT treatment and were repeated every 3 minutes over a period of 15 minutes.

The appearance of the symptom induced by postsynaptic stimulation of 5-HT_{1A} receptors is noted, and the intensity is scored using an intensity scale in which: 0 = absent, 1 = equivocal, 2 = present and 3 = intense. Behavioural scores for treated rats are accumulated throughout the observation time (5 observation periods) and expressed as mean values of 4 rats/dose. Change in mean values of treated animals in comparison with control (vehicle) group, expressed as per-cent inhibition, was used to quantify the antagonistic activity.

CLAIMS

1. A compound having the general formula I



wherein

R represents a hydrogen atom or one or more halogen atoms or (C₁-C₆)-alkyl, (C₁-C₆)-alkoxy, (C₁-C₆)-alkylthio, hydroxy, halo, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl, (C₁-C₆)-haloalkyl, (C₁-C₆)-haloalkoxy, (C₁-C₆)-hydroxyalkyl, alkoxy-(C₁-C₆)-alkyl, nitro, amino, (C₁-C₆)-aminoalkyl, (C₁-C₆)-alkylamino, N-(C₁-C₆)-alkylamino-(C₁-C₆)-alkyl, N, N-di-(C₁-C₆)-alkylamino, acylamino, (C₁-C₆)-alkylsulphonylamino, aminosulphonyl, (C₁-C₆)-alkylaminosulphonyl, cyano, aminocarbonyl, N-(C₁-C₆)-alkylaminocarbonyl, N, N-di-(C₁-C₆)-alkylaminocarbonyl, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, alkylcarbonyl-(C₁-C₆)-alkyl, formyl, alkanoyloxy-(C₁-C₆)-alkyl, (C₁-C₆)-alkylaminocarbonylamino, (C₁-C₆)-alkylsulphinyl, (C₁-C₆)-alkylsulphonyl, and N, N-di-(C₁-C₆)-alkylaminosulphonyl groups;

R₁ represents a hydrogen atom or a cycloalkyl, aryl, aryloxy, aralkyl, aralkoxy, heterocyclic, heterocycloxy, heterocycloalkyl or heterocycloalkoxy group, each group being optionally substituted with one or more substituent R as above defined;

Q represents a carbonyl or hydroxymethylene group or a group of the formula -CH(OR₂)- where R₂ represents a (C₁-C₆)-alkyl, (C₂-C₆)-alkenyl, (C₂-C₆)-alkynyl or cycloalkyl group, each of which is optionally substituted with one or more groups selected from R₈ and R₉, where R₈ is selected from the group consisting of halo, (C₁-C₆)-alkoxy, (C₁-C₆)-haloalkoxy, cyano, (C₁-C₆)-alkoxycarbonyl, (C₁-C₆)-alkylcarbonyl, alkoxyalkyl, aminocarbonyl, N-(C₁-C₆)-alkylaminocarbonyl, N, N-di-(C₁-C₆)-alkylaminocarbonyl groups and R₉ is selected from the group consisting of aryl, heteroaryl, aryloxy, heteroaryloxy, arylalkoxy, and heteroarylalkoxy groups, each optionally substituted with R, or R₂ represents -C(O)- (C₁-C₆)-alkyl, -C(O)O-(C₁-C₆)-

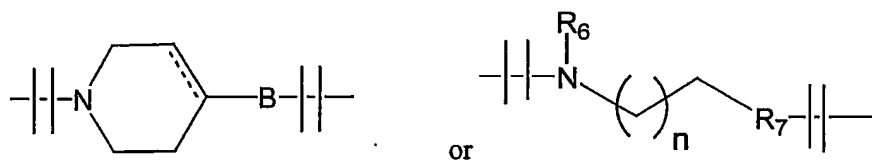
alkyl, $-\text{C}(\text{O})\text{NR}_{10}\text{R}_{11}$ or $-\text{C}(\text{S})\text{NR}_{10}\text{R}_{11}$ wherein each of R_{10} and R_{11} independently represents a hydrogen atom or a $(\text{C}_1\text{-C}_6)$ -alkyl group;

R_3 represents a $(\text{C}_1\text{-C}_6)$ -alkyl, $(\text{C}_2\text{-C}_6)$ -alkenyl, $(\text{C}_2\text{-C}_6)$ -alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted with one or more substituent R or R_1 , defined as above;

R_4 represents an aryl or heterocyclic group, each of which is optionally substituted with one or more substituents R , defined as above;

A represents CH or N ,

R_5 represents



(where R_4 is bound to the right of each group)

m and n are independently 1 or 2,

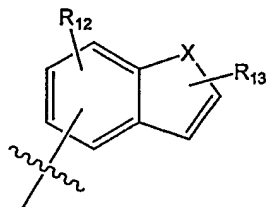
R_6 represents H or alkyl,

R_7 represents O , S , NR_6 or CH_2 ;

B represents a bond, O , S , NR_6 or CH_2 ; and

----- represents a single or double bond,

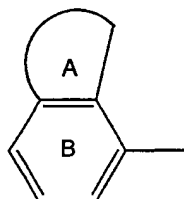
with a proviso that the substituents of formula I are not such that simultaneously Q represents $-\text{C}(\text{O})-$ or $-\text{CH}(\text{OH})-$; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, alkylthio, hydroxy, halo, haloalkyl, nitro, amino or cyano groups; R_1 represents a hydrogen atom or a phenyl or alkylphenyl group; R_3 represents a cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted with one or more substituent selected from the group consisting of $(\text{C}_1\text{-C}_6)$ -alkyl, $(\text{C}_1\text{-C}_6)$ -alkoxy, $(\text{C}_1\text{-C}_6)$ -alkylthio, hydroxy, halo, $(\text{C}_1\text{-C}_6)$ -haloalkyl, nitro, amino, cyano, unsubstituted phenyl, and alkylphenyl groups; R_5 represents group (i) wherein B represents a bond or CH_2 ; and R_4 represents the group



wherein X represents O , S , NH , $\text{N}(\text{C}_1\text{-C}_6\text{-alkyl})$, $\text{S}(=\text{O})$ or $\text{S}(=\text{O})_2$, and R_{12} and R_{13} each represent one or more member selected independently from the group consisting of halo,

hydroxy, alkyl, alkoxy, haloalkyl, alkylthio, nitro, amino, cyano, N-(C₁-C₆)-alkylamino, N, N-di-(C₁-C₆)-alkylamino, aminocarbonyl, N-(C₁-C₆)-alkylaminocarbonyl, N, N-di-(C₁-C₆)-alkylaminocarbonyl and acylamino groups, and

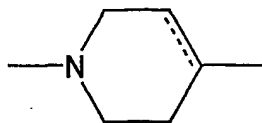
and further with the proviso that the substituents of formula I are not such that simultaneously Q represents -C(O)-; R represents a hydrogen atom or one or more substituents selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl, and alkoxycarbonyl groups; R₁ represents hydrogen; R₃ represents group (i) wherein B represents a bond or CH₂; R₄ represents an aryl or fully aromatic heteroaryl, each optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo, haloalkyl, nitro, amino, alkylamino, N, N-di-alkylamino, aminocarbonyl and alkoxycarbonyl groups; or R₄ represents a bicyclic heteroaryl radical of formula



wherein A is a saturated or unsaturated ring having one or more heteroatoms, where rings A and B are each independently substituted with one or more substituent selected from the group consisting of alkyl, halo, hydroxy, alkoxy, hydroxyalkyl, alkoxyalkyl, alkanoyloxyalkyl, alkylcarbonyl, alkylcarbonylalkyl, , amino, N-alkylamino and N,N,- di-alkylamino; and R₃ represents a saturated heterocyclic ring comprising a nitrogen atom, through which said saturated heterocyclic ring is bonded to the adjacent carbonyl group at Q, and which may optionally include a further hetero atom, and which may also be optionally substituted with one or more substituent selected from the group consisting of alkyl, alkoxy, halo and haloalkyl groups,

or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, solvate or pharmaceutically acceptable salt thereof.

2. A compound having the general formula I wherein R, R₁, R₃, R₄, R₅, Q, A and m are as defined in claim 1, provided that, if Q represents a carbonyl or hydroxymethyl group and R₅ represents a group of formula

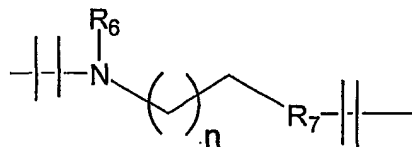


then R_3 is not a heterocyclic group attached to Q by a C-N bond and R_4 is not a substituted or unsubstituted 7-indolyl, 7-benzofuranyl or 7-benzothienyl group.

3. A compound according to claim 1 or claim 2 wherein R_5 represents



4. A compound according to claim 1 or claim 2 wherein R_5 represents



5. A compound according to any of claims 1 to 4 wherein R_3 represents a hydrogen atom or a (C_1-C_6) -alkyl, (C_2-C_6) -alkenyl, (C_2-C_6) -alkynyl group, each group being optionally substituted with one or more substituent R or R_1 as defined in claim 1.

6. A compound according to claim 5 wherein R_3 represents a hydrogen atom or a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t.butyl, vinyl, allyl, prop-1-enyl, 1-methylvinyl, 2-methylallyl, ethynyl or prop-1-ynyl group.

7. A compound according to any of claims 1 to 4 wherein R_3 represents a cyclohexyl or 2-thienyl group.

8. A compound according to any of claims 1 to 7 wherein R_4 represents an unsubstituted heterocyclic group or a phenyl group substituted with one or more halogen atoms or (C_1-C_6) -alkyl, (C_1-C_6) -alkoxy or (C_1-C_6) -haloalkoxy groups.

9. A compound according to claim 8 wherein R_4 represents a 5-(2,3-dihydro-1,4-benzodioxinyl), 4-indolyl, 8-quinolyl, 2-methoxyphenyl, 2,6-dimethylphenyl, 4-fluoro-2-

methoxyphenyl or 2-(2,2,2-trifluoroethoxy)-phenyl group.

10. A compound according to claim 1, being

- 8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-N-methyl-2-aminoethoxy}-quinoline,
- 8-{N-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-N-methyl-2-aminoethoxy}-quinoline,
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(2,6-dimethylphenyl)-piperidine,
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-hydroxybutyl]-4-(2,6-dimethylphenyl)-piperidine or
- 1-[3-(2-Cyanophenyl)-4-cyclohexyl-4-oxobutyl]-4-(4-fluoro-2-methoxyphenoxy)-piperidine.

11. A pharmaceutical composition comprising a compound according to any of claims 1 to 10 or an enantiomer, optical isomer, diastereomer, N-oxide, crystalline form, hydrate, solvate or pharmaceutically acceptable salt of such a compound in admixture with a pharmaceutically acceptable diluent, excipient or carrier.

12. A method of reducing the frequency of urinary bladder contractions in a mammal in need of such treatment, the method comprising administering an effective amount of a compound according to any of claims 1 to 10 or of a composition according to claim 11 to said mammal.

13. A method of treating neuromuscular dysfunction of the lower urinary tract in a mammal in need of such treatment, the method comprising administering an effective amount of a compound according to any of claims 1 to 10 or of a composition according to claim 11 to said mammal.

14. A method according to claim 13 whereby one or more of the conditions or symptoms of urinary urgency, overactive bladder, increased urinary frequency, incontinence, mixed incontinence, urine leakage, enuresis, dysuria, urinary hesitancy and difficulty in emptying the urinary bladder is ameliorated.

15. A method according to any of claims 12 to 14 wherein said mammal is a human.
16. A method according to any of claims 12 to 15 wherein the compound or composition is administered by an oral, enteral, intravenous, intramuscular, subcutaneous, transmucosal, transdermal or by-inhalation route.
17. A method according to any of claims 12 to 16 wherein the compound or composition is administered in combination with an antimuscarinic or α_1 antagonist.
18. A method according to claim 17 wherein said antimuscarinic is oxybutynin, tolterodine, darifenacin or temiverine.
19. A method according to claim 17 wherein said α_1 antagonist is prazosin, doxazosin, terazosin, alfuzosin or tamsulosin.
20. A method for treating disorders of the central nervous system caused by serotonergic dysfunction, the method comprising delivering an effective amount of a compound according to any one of claims 1 to 10 or of a composition according to claim 11 to the environment of a 5-HT_{1A} serotonergic receptor.
21. A method according to claim 20 wherein said compound or composition is delivered via an extracorporeal route.
22. A method according to claim 21 wherein said compound or composition is delivered by administering the compound to a mammal possessing the 5-HT_{1A} serotonergic receptor.

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
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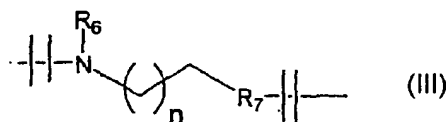
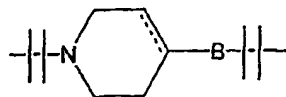
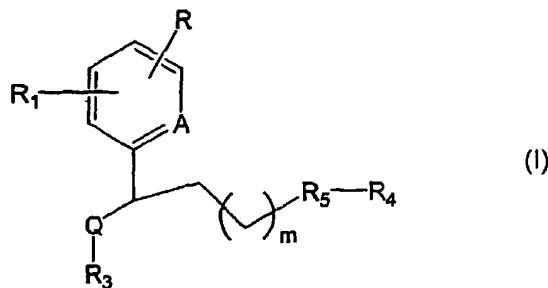
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- (74) Agent: **SERJEANTS**; 25 The Crescent, King Street, Leicester LE1 6RX (GB).
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[Continued on next page]

(54) Title: PHENYLALKYLAMINES AND PYRIDYLALKYLAMINES WITH SEROTONINERGIC RECEPTOR AFFINITY



(57) Abstract: Compounds of formula (I), (A is CH or N, R and R₁ are a wide range of substituents, Q is CO, CHOH or CHOR₂, R₂ is alkyl, alkenyl, alkynyl or cycloalkyl group, each of which is optionally substituted, or is alkanoyl, alkanoyoxy, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, aminothiocarbonyl, alkylaminothiocarbonyl or dialkylaminothiocarbonyl, R₃ is alkyl, alkenyl, alkynyl, cycloalkyl, aryl or heterocyclic group, each of which is optionally substituted, m is 1 or 2, R₄ is an aryl or heteroaryl group, either of which is optionally substituted, R₅ is either (II) or (III), wherein m is 1 or 2, R₆ is H or alkyl, R₇ is O, S, NR₆ or CH₂, B is a bond, O, S, NR₆ or CH₂ and ----- represents a single or double bond) have affinity for serotoninergic receptors. These compounds and their enantiomers, diastereoisomers, N-piperazine oxides, polymorphs, solvates and pharmaceutically acceptable salts are useful in the treatment of patients with neuromuscular dysfunction of the lower urinary tract and diseases related to 5-HT_{1A} receptor activity.



(88) Date of publication of the International search report:

17 June 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06290

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/14 C07D211/46 C07D215/26 A61K31/445 A61K31/451
A61K31/47 A61P13/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE 671 440 A (DR. KARL THOMAE GMBH) 1965 Starting material 17 in the table on page 6 corresponding to formula III on page 5	1,2,4-6
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X	US 5 585 374 A (CLIFFE IAN A ET AL) 17 December 1996 (1996-12-17) cited in the application claims; example 5	1-22
X	WO 96 16961 A (AMERICAN HOME PROD) 6 June 1996 (1996-06-06) page 5, line 23 - line 32; claims; examples 2-5	1-22
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

1 April 2004

Date of mailing of the international search report

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Hanisch, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06290

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 610 164 A (BAUDY REINHARDT B ET AL) 11 March 1997 (1997-03-11) column 3, line 11 - line 29; claims; example 2 -----	1-22
X	EP 0 982 304 A (LILLY CO ELI) 1 March 2000 (2000-03-01) cited in the application claims 1-15,18-32; examples 1-52 -----	1-22
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X	EP 0 924 205 A (LILLY CO ELI) 23 June 1999 (1999-06-23) paragraph '0010!; claims 1-16; examples 1-4,6-8 -----	1-22

INTERNATIONAL SEARCH REPORT

national application No.
PCT/EP 03/06290

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 12-22 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Initial Application No

PCT/EP 03/06290

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06290

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